

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 10 and 27-157¹ are pending in the application. Claims 10, 27-94 and 148-157 have been withdrawn from examination by the Examiner. Thus, claims 95-147 are currently under examination. Claims 95, 98, 101, 104, 115 and 117 have been amended to remove a trademark designation from the claims as requested by the Examiner. The specification has been amended to correct typographical errors. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 95-126 under 35 U.S.C. § 112, second paragraph, as being indefinite due to the trademark "Bestfit®." Applicants respectfully traverse the rejection.

¹ On form PTO-326 and on page 2 of the Office action, the Examiner indicated that claims 95-147 are pending in the application. Applicants assert that claims 10 and 27-157 are currently pending. Claims 10, 27-94 and 148-157 have been withdrawn from examination, but have not been canceled.

The Examiner suggested that Applicants remove the trademark from the claims. Applicants appreciate the Examiner's suggestion and have removed the trademark from the claims. The removal of the "Bestfit®" trademark from the claims is for clarity and does not narrow the claims in any way. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 101

The Examiner rejected claims 95-147 under 35 U.S.C. § 101 "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility" (Office action, page 4). More specifically, the Examiner asserted that the claims are "drawn to an invention with no apparent or disclosed patentable utility. . . . The instant application has provided a description of a nucleotide to a partially isolated protein. However, the instant application does not disclose the biological role of this protein or its significance" (Office action, page 4). Applicants respectfully traverse the rejection.

The Examiner further asserted that:

the claimed polynucleotide encodes an 'orphan receptor' in the art. There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicants' claimed invention is incomplete.

. . .

The instant claims are drawn to a polynucleotide encoding a protein which has a yet undetermined function or biological significance. Applicants have hypothesized that this receptor is a member of the GABA receptor family of receptors. There is no actual and specific significance which can be attributed to said protein identified in the specification. Applicants have not disclosed that they are in possession of compounds which interact with this subunit of

a GABA receptor, or that this subunit has activity. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it.

Office action, pages 4-5.

To satisfy the requirements of 35 U.S.C. § 101, the invention must have a well-established utility *or* Applicants must assert a credible, specific and substantial utility for the invention. If an applicant asserts that the invention is useful for *any* particular practical purpose that is credible, then a rejection based on lack of utility should not be imposed. *See* Utility Examination Guidelines (Federal Register, vol. 66(4): 1098 (col. 2) (Jan. 5, 2001)). Furthermore, Applicants need only make one credible assertion of specific utility for the claimed invention to satisfy the utility requirements of 35 U.S.C. §§ 101 and 112. *See, e.g., Raytheon v. Roper*, 724 F.2d 951, 958, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984).

In reviewing the specification to determine if an applicant has asserted a credible, particular practical purpose, examiners must “distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful” (emphasis in the original) (MPEP § 2107(I) (7th Ed., Rev. 1, Feb. 2000)).

In the current application, Applicants have asserted that the GABA_A receptor ϵ subunit protein (GABRE) and ET2 protein (alternative transcript of GABRE) have utility beyond that of a probe or primer. More specifically, Applicants have established that a

credible, particular practical purpose exists for these proteins since Applicants have disclosed specific biological activities.

As noted in the MPEP (7th Ed., Rev. 1 (Feb. 2000)) § 2107(III):

pharmacological or therapeutic inventions that provide any 'immediate benefit to the public' satisfy 35 U.S.C. 101. The utility being asserted in *Nelson* related to a compound with pharmacological utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980). Office personnel should rely on *Nelson* and other cases as providing general guidance when evaluating the utility of an invention that is based on any therapeutic, prophylactic, or pharmacological activities of that invention.

MPEP, page 2100-26. In *Nelson v. Bowler*, the court stated that:

[k]nowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that the *adequate proof of any such activity constitutes a showing of practical utility*.

Nelson at 856 (emphasis added). Applicants' situation is analogous to that described in *Nelson* as Applicants have established that the claimed polynucleotides have pharmacological activity. This is in direct contrast to Example 9 (DNA fragments with no indicated activity) in the Revised Interim Utility Guidelines Training Materials upon which the Examiner appears to have based this rejection.

The GABA receptor complex² can be regulated by drug-induced modulations and thus, it is a primary site of action for certain drugs used to treat anxiety and seizure disorders, for example. As noted in the specification, page 3, lines 1-2, “[v]ariations in subunit combinations can result in different pharmacological properties being conferred upon the receptor complex.” More specifically, as discussed on page 54, lines 25-26, of the specification, varying the subunit composition of the receptor complex can result in altered ligand induced responses. For example, “the presence of a GABRE subunit inhibits the ability of anesthetic agents to potentiate GABA-gated chloride currents” and the presence of ET2 is believed to alter “the binding affinity of this [receptor] complex to various ligands” (specification, page 55, lines 2-6). Applicants have provided data to support this assertion. See Example 6 in the specification, wherein Applicants demonstrate that “the presence of the ϵ -subunit had a pronounced effect on the sensitivity of GABA_A receptors to intravenous anaesthetic agents” (page 97, lines 6-8). Figures 6A-6D demonstrate this effect *via* radioligand binding and GABA-evoked current measurement. See also Davies *et al.*, *Nature* 385: 820-823 (February 1997) (cited by the Examiner in the March 27, 2000, Office action). In addition, GABRE and ET2 likely enhance the binding affinity of the receptor complex to ligands when the ligands do not generally bind to the complex with high affinity. Thus, contrary to the Examiner’s position, Applicants have described and verified by

² GABRE and ET2 are polypeptides belonging to the ligand-gated ion channel gene superfamily. Members of this superfamily mediate synaptic inhibition of neuronal activity in the mammalian brain through the neurotransmitter γ -aminobutyric acid (GABA). GABA binds to a receptor complex which opens channels across the neuronal cell membrane. Anions, such as chloride, then move down their concentration gradients through this membrane. The receptor complex is made up of subunits. GABRE and ET2 are such GABA receptor subunits. More specifically, they are members of the epsilon subunit which is expressed abundantly in the subthalamic nucleus.

experimental data specific pharmacological activities of the polypeptide encoded by the claimed polynucleotides. This is all that is required to satisfy 35 U.S.C. § 101. Thus, Applicants have provided *specific* statements as to why the invention is considered useful in the "real world," and not mere indications that the invention may prove useful.

The Examiner has the burden of providing documentary evidence or at least scientific reasoning for why the Examiner doubts the utility set forth in the specification (Utility Guidelines, Federal Register, vol. 66(4): 1098 (Jan. 5, 2001)). Since the Examiner has not provided such documentary evidence or scientific reasoning, and since Applicants have set forth at least one credible, specific and substantial utility, the requirements of 35 U.S.C. § 101 have been satisfied. Thus, Applicants assert that the rejection is in error and withdrawal thereof is respectfully requested.

Objection to the Specification and Rejection under 35 U.S.C. § 112, first paragraph (utility)

The Examiner objected to the specification and rejected claims 95-147 under 35 U.S.C. § 112, first paragraph, for failure to teach how to use the invention based on the rejection under 35 U.S.C. § 101. Applicants respectfully traverse the rejection.

The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." MPEP § 2107(IV) (7th Ed., Rev. 1, Feb. 2000). Therefore, since the claims comply with the utility requirement of 35 U.S.C. § 101 as indicated above, the rejection under 35 U.S.C. § 112, first paragraph, based on lack of utility, should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner rejected claims 95, 98, 101, 104, 107-117, 119-126 and 127-147 under 35 U.S.C. § 112, first paragraph,

because the specification, while being enabling for SEQ ID NO:42 does not reasonably provide enablement for polypeptides which are 'at least 95% identical' to various amino acid segments of SEQ ID NO:42. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Office action, page 6. More specifically, "the Examiner holds that undue experimentation would be necessary to practice the method of using fragments and segments of SEQ ID NO:42 as claimed" (Office action, page 7). Applicants respectfully traverse the rejection.

The Examiner stated that the phrase "at least 95% identical" renders the breadth of the claims "too large" since "Applicants have only provided guidance and working examples of the claimed segments of SEQ ID NO:42 and not of proteins which are at least 95% identical to various segments of SEQ ID NO:42" (Office action, page 6). The Examiner further stated that, "it is not predictable to one of ordinary skill in the art what proteins which only comprise at least 95% identity to the disclosed segments of SEQ ID NO:42 would code for" (Office action, pages 6-7).

Applicants first note that the Examiner has drafted the rejection based on claimed polypeptides. However, polynucleotides are claimed, not polypeptides. Applicants are not required to demonstrate enablement for unclaimed material.

Assuming that the Examiner intended "polynucleotides," the Examiner's position suggests that Applicants have not provided sufficient information regarding what polynucleotides are intended by the phrase "at least 95% identical." The plain and ordinary meaning of this phrase is clear in that the claims encompass polynucleotides with less than or equal to 5% differences between the reference sequence and the second sequence. Since the meaning of "at least 95% identical" is clear, one skilled in the art would readily be able to determine what sequences are 95% identical and thus, what polynucleotides are encompassed by the claims.

There are at least two methods of determining percent identity. First, the specification teaches,

[b]y a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding an ET2 or GABRE polypeptide is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the ET2 or GABRE receptor subunit. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence.

Specification, page 22, lines 9-19. The differences can be located at either end of the reference sequence or anywhere in between, and they can be distributed individually or in contiguous groups. *See* specification, page 22, lines 19-23. Thus, if the reference sequence and a second sequence have less than or equal to 5% differences, i.e., a total of, at most, five deletions, insertions and substitutions per 100 residues of the reference sequence, then the

second sequence falls within the scope of the claim. If there are more than five differences per 100 residues of the reference sequence, then the second sequence is not encompassed by the scope of the claim. One of ordinary skill in the art could easily align two highly identical sequences "by eye" or "manually," i.e., without a computer. By manually aligning SEQ ID NO:41, for example, with a second, highly identical sequence, the skilled artisan could count the deletions, insertions and substitutions in the second sequence and calculate the percent identity. Thus, the scope of claims reciting at least 95% identity is clear.

Second, although a computer program is not necessary, the specification teaches that,

[a]s a practical matter, whether any particular nucleic acid molecule is at least 95%, 96%, 97%, 98% or 99% identical to, for instance, the nucleotide sequence shown in SEQ ID NO:1 or SEQ ID NO:41 can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). Bestfit uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics* 2:482-489 (1981), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed.

Specification, page 22, line 24, to page 23, line 8.

Although a computer program is not necessary to determine whether a highly homologous sequence falls within the scope of the claimed polynucleotides, the specification recites language explaining the computed-based method used to determine percent identity. The pending claims recite sequences with 95% or more identity to a

reference sequence, wherein the percent identity is calculated with specified parameters. The specification refers to the fact that the Bestfit® program can be used. This program uses an algorithm disclosed in Smith and Waterman, *Advances in Applied Mathematics* 2:482-489 (1981) (specification, page 23, lines 1-2.) Thus, the skilled artisan would immediately recognize how to determine percent identity, and would understand what is encompassed by the claims and how to practice the invention. Thus, one skilled in the art could routinely make and use the polynucleotides falling within the full scope of the claims as it can be readily determined what polynucleotides are encompassed by the claim language.

Regarding claims 136-147, the Examiner asserted that "the breadth of the claims is too large with regard to the claimed fragments of SEQ ID NO:42. First the specification does not provide any guidance or working examples of the use of fragments of SEQ ID NO:42 and it is not predictable to one of ordinary skill in the art which fragments of SEQ ID NO:42 can be used or how to use them" (Office action, page 7).

The Examiner is of the position that the alleged failure of the specification to recite each and every possible sequence encompassed by the claims renders the claims non-enabled. However, a specification need not disclose each and every operative example of a class of compounds when the skilled artisan is fully apprised by the disclosure of what the invention is and how to use it. *In re Boller*, 332 F.2d 382 (CCPA 1964). Moreover, according to MPEP (7th Ed., Rev. 1 (Feb. 2000)) § 2164.02, "because only an enabling disclosure is required, applicant need not describe all actual embodiments." Thus, the fact that there are undisclosed sequences that are encompassed by the claims does not automatically render the claims non-enabled.

Regarding the Examiner's comment pertaining to unpredictability in the art of how to make and use fragments, the skilled artisan is well-versed in the creation of variant sequences, including fragments, when a reference sequence is provided. The Examiner even stated on page 8 of the Office action, "these types of changes [creating variants] are routinely done in the art." The Examiner further stated on page 8 that, "the specification and claims do not provide any guidance as to what changes should be made." However, Applicants have provided guidance. For example, on page 25 of the specification, Applicants refer to polynucleotide variants caused by the degeneracy of the genetic code and to variants caused by nucleotide substitutions. Determining appropriate substitutions, deletions, etc. is well-within the purview of the skilled artisan and, as such, detailed guidance is not required by Applicants. A patent specification preferably omits what is well-known in the art (MPEP § 2164.01). Further, it must be remembered that the polynucleotides encompassed by the claims have ET2 or GABRE activity as disclosed on pages 23-25 of the specification. The inclusion of critical nucleotides related to amino acid and thus, protein function is addressed at page 36, lines 6-15.

As suggested by the Examiner, the issue boils down to undue experimentation. Would it require undue experimentation to determine the encompassed, but not specifically taught, sequences? The answer is no. The test for undue experimentation is "not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue" (MPEP (7th Ed., Rev. 1 (Feb. 2000)) § 2164.01). Experimentation to practice the claimed invention using the specification as guidance along with what is known in the art is to be expected. As noted in *In re Wands*, a considerable amount of experimentation is permissible if it is merely routine. *In re Wands*, 8 USPQ2d 1400, 1404 (1988). Since the specification

provides considerable guidance regarding how to practice the invention, i.e., the methods required to practice the invention are either known or set forth in the specification, the skilled artisan would have no difficulty determining the sequences encompassed by the claims. Thus, the experimentation required is routine, not undue.

Applicants submit that all of the claims meet the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejected claims 95, 98, 101, 104, 107-117 and 119-126 under 35 U.S.C. § 112, first paragraph, “as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention” (Office action, page 7). Applicants respectfully traverse the rejection.

The Examiner asserted that the rejected claims are “genus claims” and that:

[t]he specification and claims do not indicate what distinguishing attributes are shared by members of the genus. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although these types of changes are routinely done in the art, the specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

Office action, pages 7-8. The Examiner concluded that the disclosure does not set forth "a representative number of species to describe the genus" (Office action, page 8).

The adequate written description requirement serves to ensure that the inventor had possession, as of the filing date, of the claimed subject matter. However, "how the specification accomplishes this is not material." *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). "If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *In re Alton*, 37 U.S.P.Q. 2d 1578, 1584 (C.A.F.C. 1996).

In the present case, the Examiner asserted that one skilled in the art would not conclude that Applicants were in possession of the claimed genus due to the alleged absence of common structural attributes or characteristics of the genus. Applicants assert that disclosure of the *entire* open reading frame of the GABA receptor protein, in addition to the fragments of SEQ ID NO:41 encoding amino acids 1-260, 1-488, -17 to 488 and -18 to 488 of SEQ ID NO:42, is representative of the genus of polynucleotides encompassed by the claims.

Additionally, one skilled in the art can readily envisage nucleic acid sequences which include fragments of SEQ ID NO:41 or which encode fragments of SEQ ID NO:42, because, for example, SEQ ID NO:41 can be readily embedded in known vectors. Although there may be variability among the species of polynucleotides encompassed within the scope of the claims, the necessary common structural feature remains, i.e., SEQ ID NO:41 or fragments thereof.

Moreover, Applicants note that, according to the USPTO's written description guidelines, "[t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by . . . disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties . . ." (Written Description Guidelines, Federal Register, vol. 66(4): 1106 (col. 3) (Jan. 5, 2001)). Applicants submit that the disclosure of the specific sequences recited above, which are members of the claimed genus, is sufficient to satisfy the written description requirement because *these sequences are representative of the genus*. For example, polynucleotides which comprise sequences 95% identical to the specific sequences disclosed, or are identical to such sequences, will show activity much like the specifically disclosed polynucleotides as described above. Moreover, members of the genus will share many of epitopic regions of the reference polynucleotides. Thus, polynucleotides comprising the specific sequences are exemplary of the structure of the variants within the genus. It must be remembered that the "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces" (Written Description Guidelines, Federal Register, vol. 66(4): 1106 (col. 3) (Jan. 5, 2001)).

In *Regents of the University of California v. Eli Lilly & Co.*, 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997), *cert. denied*, 66 U.S.L.W. 3688 (1998) (hereinafter "*Eli Lilly & Co.*"), the court stated that, "[a] description of a genus of cDNAs may be achieved by means of a recitation of [1] a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus *or* [2] a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. . . ." *Eli*

Lilly & Co., 43 U.S.P.Q.2d at 1406 (emphasis added). Thus, the Federal Circuit has indicated that the written description requirement for generic claims directed to genetic material, such as cDNA, may be satisfied by providing the sequences of a representative number of nucleic acids which fall within the scope of the genus *or* by providing a recitation of common structural features of the members of the genus. For the reasons stated above, Applicants assert that, to the satisfaction of the first test set forth in *Eli Lilly & Co.*, the reference polynucleotides are representative of the claimed genus.

In addition, Applicants assert that, as mandated by the Federal Circuit, the disclosure of the complete nucleotide and amino acid sequences of the reference sequences, epitopic regions within the reference sequences (described on pages 40-42 of the specification), and the structural domains which comprise the reference sequences constitutes a recitation of the structural features common to the members of the genus. For example, the recitation of the nucleotide sequence of the reference polynucleotides is a recitation of the structural features common to the members of the genus because the polynucleotides included within the genus will have at least 95% of their nucleotide sequence (primary structure) in common with each other (and to the reference polynucleotides).

Further, the reference polynucleotides may share in common with the other members of the genus specific epitopic regions capable of generating antibody as well as other structural regions such as the extracellular, intracellular and transmembrane domains. Moreover, one skilled in the art would be able to visualize and recognize innumerable members of the genus given the disclosure of the nucleotide and related amino acid sequences of the reference polynucleotides and the location and characterization of important regions within the polynucleotides. Thus, Applicants assert that to the satisfaction

of the second test set forth in *Eli Lilly & Co.*, the specification has satisfied the requirements for written description.

Applicants submit that all of the claims meet the written description requirement. Accordingly, withdrawal of this rejection is respectfully requested.

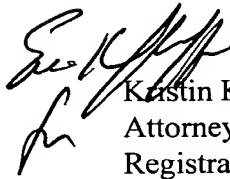
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully
requested.

Respectfully submitted,

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Version with markings to show changes made

Specification:

The paragraph beginning on page 3, line 1:

Variations in subunit combinations can result in different pharmacological properties being conferred upon the receptor complex (Davies, P.A. *et al.*, *Nature* 385:820-823 (1997); reviewed in Whiting, P.J. *et al.*, *Int. Rev. Neurobiol.* 38:95-138 (1995)). Thus, subpopulations of GABA_A receptor complexes show differing sensitivity to GABA, steroid modulators, physiological regulation, disease processes, and pharmacological manipulation by drugs (*e.g.*, benzodiazepines). The distributions of mRNAs encoding different GABA_A receptor subunit polypeptides and their subtypes localized in the brain show significant regional variation consistent with pharmacological and biochemical evidence for receptor heterogeneity. Further, alterations in brain specific expression of GABA_A receptor complex subunit polypeptides [has] have been identified in human brain tissues of individuals suffering from alcoholism (Lewohl, J. *et al.*, *Brain Res.* 751:102-112 (1997)).

The paragraph beginning on page 6, line 3:

The invention further provides [an] isolated polypeptides having an amino acid sequence selected from the group consisting of: (a) the amino acid sequence of the ET2 polypeptide having the complete 242 amino acid sequence; (b) the amino acid sequence of the GABRE polypeptide having the complete 506 amino acid sequence; (c) the amino acid sequence of the ET2 polypeptide having the complete 242 amino acid sequence but minus the N-terminal methionine residue; (d) the amino acid sequence of the GABRE polypeptide having the complete 506 amino acid sequence but minus the N-terminal methionine residue; (e) the amino acid sequence of the mature GABRE protein; (f) the amino acid sequence of one or more ET2 or GABRE transmembrane domains; (g) the amino acid sequence of the ET2 or GABRE intracellular domain; (h) the amino acid sequence of the GABRE extracellular domain; and (i) the amino acid sequence of the ET2 or GABRE protein with all or part of one or more of the transmembrane domains deleted.

The paragraph beginning on page 16, line 1:

In another aspect, the invention provides isolated nucleic acid molecules encoding the GABRE polypeptide having an amino acid sequence as encoded by the cDNA clone contained in the plasmid deposited as ATCC Deposit No. 209642 on February 25, 1998. In a further aspect, nucleic acid molecules are provided encoding the full-length ET2 or GABRE polypeptide lacking the N-terminal methionine. The invention also provides an isolated nucleic acid molecule having the nucleotide sequence shown in SEQ ID NO:1 or SEQ ID NO:41, or a nucleic acid molecule having a sequence complementary to that of SEQ ID NO:1 or SEQ ID NO:41. Such isolated molecules, particularly DNA molecules, are useful as probes for gene mapping, [by] for *in situ* hybridization with chromosomes, and for detecting expression of ET2 or GABRE nucleotide sequences in human tissue, for instance, by Northern blot analysis.

The paragraph beginning on page 18, line 16:

In another aspect, the invention provides isolated nucleic acid molecules comprising polynucleotides which [hybridizes] hybridize under stringent hybridization conditions to a portion of the polynucleotide in a nucleic acid molecule of the invention described above, for instance, the cDNA sequences shown in SEQ ID NO:1 and SEQ ID NO:41, or the cDNA clone contained in ATCC Deposit No. 209642. By "stringent hybridization conditions" is intended overnight incubation at 42°C in a solution comprising: 50% formamide, 5x SSC (750 mM NaCl, 75mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

The paragraph beginning on page 55, line 23:

By "agonist" is intended naturally occurring and synthetic compounds capable of enhancing one or more activity of the ET2 and/or GABRE receptor subunit. Such agonists include modified forms of the ET2 or GABRE polypeptide and agents which increase

expression of ET2 and/or GABRE receptor subunits. By "agonistic activity" is intended the enhancement of one or more ET2 and/or GABRE receptor subunit activities. By "antagonist" is intended naturally occurring and synthetic compounds capable of inhibiting one or more [activity] activities of the ET2 and/or GABRE receptor subunit. Such antagonists include modified forms of the ET2 or GABRE polypeptide and agents which decrease expression of ET2 and/or GABRE receptor subunits. By "antagonistic activity" is intended the inhibition of one or more ET2 and/or GABRE receptor subunit activities. Whether any candidate "agonist" or "antagonist" of the present invention can enhance or inhibit ET2 and/or GABRE receptor subunit activity can be determined using art-known assays, including those described in more detail below.

Claims:

95. (twice amended) An isolated polynucleotide comprising a nucleotide sequence encoding an amino acid sequence at least 95% identical to amino acids 1 to 260 of SEQ ID NO:42;

wherein % identity is determined [using the Bestfit[®] program] with parameters that calculate % identity over the full length of amino acids 1 to 260 of SEQ ID NO:42 and that allow gaps of up to 5% of the total number of amino acid residues in amino acids 1 to 260 of SEQ ID NO:42.

98. (twice amended) The isolated polynucleotide of claim 95, wherein said amino acid sequence is at least 95% identical to amino acids 1 to 488 of SEQ ID NO:42;

wherein % identity is determined [using the Bestfit[®] program] with parameters that calculate % identity over the full length of amino acids 1 to 488 of SEQ ID NO:42 and that

allow gaps of up to 5% of the total number of amino acid residues in amino acids 1 to 488 of SEQ ID NO:42.

101. (twice amended) The isolated polynucleotide of claim 98, wherein said amino acid sequence is at least 95% identical to amino acids -17 to 488 of SEQ ID NO:42; wherein % identity is determined [using the Bestfit® program] with parameters that calculate % identity over the full length of amino acids -17 to 488 of SEQ ID NO:42 and that allow gaps of up to 5% of the total number of amino acid residues in amino acids -17 to 488 of SEQ ID NO:42.

104. (twice amended) The isolated polynucleotide of claim 101, wherein said amino acid sequence is at least 95% identical to amino acids -18 to 488 of SEQ ID NO:42; wherein % identity is determined [using the Bestfit® program] with parameters that calculate % identity over the full length of amino acids -18 to 488 of SEQ ID NO:42 and that allow gaps of up to 5% of the total number of amino acid residues in amino acids -18 to 488 of SEQ ID NO:42.

115. (twice amended) An isolated polynucleotide comprising a nucleotide sequence encoding an amino acid sequence at least 95% identical to the mature amino acid sequence encoded by the cDNA clone in ATCC Deposit No. 209642, wherein % identity is determined [using the Bestfit® program] with parameters that calculate % identity over the full length of the mature amino acid sequence encoded by the cDNA clone in ATCC Deposit No. 209642 and that allow gaps of up to 5% of the total

number of amino acid residues of the mature amino acid sequence encoded by the cDNA clone in ATCC Deposit No. 209642.

117. (twice amended) The isolated polynucleotide of claim 115, wherein said amino acid sequence is at least 95% identical to the complete amino acid sequence encoded by the cDNA clone in ATCC Deposit No. 209642;

wherein % identity is determined [using the Bestfit® program] with parameters that calculate % identity over the full length of the complete amino acid sequence encoded by the cDNA clone in ATCC Deposit No. 209642 and that allow gaps of up to 5% of the total number of amino acid residues of the complete amino acid sequence encoded by the cDNA clone in ATCC Deposit No. 209642.